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7590 12/17/2003				
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		EXAMINER		
		SHUKLA, RAM R		
		ART UNIT		PAPER NUMBER
		1632		

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/407,402

Applicant(s)

NATESN ET AL.

Examiner

Ram R. Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-67 is/are pending in the application.
- 4a) Of the above claim(s) 1-38 and 52-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 39-51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 September 1999 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicants' response filed 3-17-03 and 9-15-2003 has been received and entered.

1. As noted in the previous office action of 9-11-02, Applicant's election with traverse of the invention of group II (Claims 39-51) in Paper No. 11 is acknowledged and was made final in the previous office action of 9-11-02 and the finality is maintained. Applicants' argument that the restriction of 1-23-02 indicated that claims 1-38 would be examined together with group II is not correct. What was stated regarding claims 1-38 in the restriction requirement of 1-23-02 is restated below:

"3. The embodiments recited in claims 1-38 are common to the inventions of the groups II-V. Should any of these groups be elected, claims 1-38 would be examined to the extent they read on the elected invention."

This meant that claims 1-38 would be examined to the extent they were required for the inventions of groups II-V.

Next applicants argue that the invention of group II is not just a cell. Likewise, applicants argue that invention of group V is not just an organism. While applicants point is well taken, the description of an invention in a restriction requirement is a brief description and therefore cannot describe all the features of the invention. Applicants arguments that the two groups contain logical subject matter and should be examined together is not persuasive because of the reasons of record set forth in the office actions of 1-23-02 and 9-11-02 that the two inventions are patentably distinct and will require separate non-coextensive searches.

Applicants' arguments that those various nucleic acids of group I are the same nucleic acids references in claims dependent on group I claims and therefore should be considered together are not persuasive. While there may be some overlapping search, such search will not be coextensive. It is emphasized that it is not only the search but also examination that determines restriction (see MPEP 803). In the instant case, both search and examination of different inventions will be burdensome.

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With regard to applicants' arguments that the search must encompass all required elements, it is noted that keeping this same principle in mind the examiner had indicated that claims 1-38 will be examined to the extent they are encompassed by the elected invention.

2. Claims 1-38 and 52-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. This application contains claims 1-38 and 52-67 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 39-51 remain objected to because they are dependent on withdrawn claims.

5. Amendments to the specification inserting SEQ ID NOs have been entered.

### ***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for rendering a cell capable of expressing a target gene in a cell in a ligand dependent manner by transducing the cell with a recombinant nucleic acid that comprises a p65 domain comprising a part or all of the amino acids spanning from 361 to 550 of human NF- $\kappa$ B p65 alone or as a fusion with the VP16 V8, VP16 V9, VP16 C, HSF or CTF activation domain and a ligand binding domain, wherein the ligand binding domain is a progesterone or ecdysone receptor derived ligand binding domain; or wherein

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the recombinant nucleic acid further comprises a DNA binding domain and an isolated mammalian cell comprising a target gene construct comprising the target gene and the recombinant nucleic acid, does not reasonably provide enablement for a method wherein the cell is present in vivo in an animal for reasons of record set forth in the previous office action of 9-11-2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope rejection has been modified in view of the inadvertent error in the previous rejection as indicated by the applicant.

### ***Response to Arguments***

Applicant's arguments filed 3-17-2003 have been fully considered but they are not persuasive. Applicants have argued that genetic engineering of animals was reliably carried out by those of ordinary skill in the art. Applicants argue that for gene delivery, the art was already aware of the vector systems. In the support of their arguments, they different word documents, patents and research articles. However, these arts do not change the unpredictable nature of the in vivo method of gene delivery. While the arts cited by the applicant may provide support for a specific method, unique to the subject of the cited art, they do not provide enablement for a general method of in vivo gene therapy and gene delivery. Applicants' listing of documents does not address any of the specific issues raised in the last office action and the issues raised in the arts showing the state of the art of gene therapy at the time of the invention. Next, applicants argue that no particular level is required by the pending claims, however, these arguments are not persuasive since without expression what is the purpose of the in vivo delivery. Regarding applicants arguments that present claims are not limited to but encompass therapeutic application of the invention method and that even if some particular therapeutic method is not enabled, applicant is not required to enable every species that falls within the scope of the claim. Again, these arguments are not persuasive because the unpredictability of a particular area may alone provide

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reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

Additionally, courts have stated:

"However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In *re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In *re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In *re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In *re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work."

8. The 35 U.S.C. 112 second paragraph rejections of claims 39-51 have been withdrawn in view of applicants' response.

### ***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 39, 41, 43-45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz et al. (The EMBO Journal 10:3805-3817, 1991).

Schmitz et al. teach recombinant DNA molecules encoding polypeptides comprising a DNA-binding domain of GAL4 protein and portions of human NF-κB p65 comprising residues from the regions 361-450 and 361-550 (pp. 3808-11). Schmitz et al. also teach co-transfection of cells with said DNA molecules and a CAT reporter construct with GAL4-binding sites in the promoter region. Schmitz et al. further teach that residues 521-550 of NF-κB comprise a strong transactivating domain, TA<sub>1</sub>, and that a second transactivating domain, TA<sub>2</sub>, is present in residues 441-518 (p. 3809).

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 39-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al and Schmitz et al in view of Evans et al (US 5,597,693; US 5,262,300 and US 5534,418; US 6,635,429).

Fishman et al. teaches a regulatable gene expression system comprising (1) a tet repressor-VP16 transactivator expression plasmid and (2) a luciferase expression plasmid comprising a tet operator in its promoter region. Fishman et al. teach injection of said plasmids into cardiac muscle of a rat and show that oral tetracycline efficiently induces expression of the luciferase gene in the treated rat's cardiac cells (pp. 1864-6).

Schmitz et al. teach making recombinant DNA molecules encoding fusion transcription factors comprising a DNA-binding domain of GAL4 protein and a portion of NF- $\kappa$ B p65 comprising transactivating domain TA<sub>1</sub>, located in residues 521-550, or TA<sub>2</sub> located in residues 441-518, and a method wherein cells are co-transfected with one of said DNA molecules and with a CAT reporter construct

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having GAL4-binding sites in the promoter region to effect expression of the reporter gene in said cells, as discussed above. Schmitz et al. also teach that a chimeric transcription factor consisting of the DNA-binding domain of GAL4 protein and the transactivating domain of VP16 is a stronger inducer of transcription than any of the GAL4-p65 constructs which they tested (p. 3810).

Fishman et al. and Schmitz et al. do not teach constructs wherein the DNA-binding domain is a domain of a human protein or is a composite DNA-binding domain, or wherein the transcription factor comprises a composite transactivation domain such as a fusion comprising transactivation domains from both human NF- $\kappa$ B p65 and VP-16.

Evans et al. (US Pat. 5,597,693) teach that domains of steroid receptors are interchangeable, and that the DNA-binding domain of the human glucocorticoid receptor can be replaced by that of the thyroid hormone receptor to produce a hybrid protein which binds and activates promoters comprising a thyroid hormone receptor response element (col. 9, lines 40-43). They also demonstrate that a transcription factor comprising a composite DNA-binding domain made up of portions of two different human steroid receptors functions effectively in cells to activate a gene promoter comprising a response element which is recognized by said composite DNA-binding domain (Example 2, columns 9-10).

Evans et al. (US Pat. 5,262,300) disclose transcription factors having a composite transactivating domain comprising (a) multiple copies of one or more transactivating regions of a given human steroid receptor, or (b) a transactivating region of a human steroid receptor and also comprising a synthetic acidic peptide which has transactivating activity, and they show that both types of transcription factors function effectively in cells to activate a gene promoter comprising a response element which is recognized by said transcription factors (column 12, line 46, to col. 13, line 9).

Evans et al. (US Pat. 5,534,418) teach using a gene expression system comprising (a) a vector encoding a steroid receptor-type transcription factor, and (b) an expression plasmid comprising in its promoter a response element which is bound by the DNA-binding domain of said steroid receptor-type transcription factor,

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to obtain regulated expression of the gene encoded by said expression plasmid (b) in cells of an animal (col.s 19-20).

Evans et al (US 6,265,173) teaches expression system using the DNA binding domain of thyroid-steroid family hormone receptors, which include steroid receptors, RAR, progesterone receptor, RXR receptors to name a few (see columns 4-6).

At the time the application was filed, it would have been obvious to one of ordinary skill in the art to modify the vector of Fishman et al and Schmitz et al to make a vector that comprises a nucleic acid encoding a transcription factor comprising a DNA-binding domain of a steroid hormone, such as progesterone hormone, or ecdysone receptor or other hormones taught by Evans et al and an activation domain that will comprise full length or fragment of p65, given the teaching of Evans et al. that such sequence-specific DNA-binding domains can be interchanged between proteins with retention of function and that a transcription factor comprising a composite DNA-binding domain or a composite transactivating domain functions more effectively to activate transcription in a cell.

It would have been obvious to one of ordinary skill in the art to make a vector wherein the transcription factor comprises NF- $\kappa$ B p65, and the DNA binding domain of tetracycline responsive transactivator tetR, given the teachings of Fishman et al and Schmitz et al. by replacing the VP16 activation domain with p65 to determine its transactivation activity in association with other DNA binding domains. It is noted that Schmitz et al teaches that vp16 when associated with GAL4 DNA binding domain showed stronger activity than GAL4-p65. Therefore, a possibility of stronger transactivation by p65 when GAL-4 DNA binding domain was replaced with tetR binding domain would have been provided motivation to exchange the GAL4 domain with tetR. Thus, the invention as a whole stands as being clearly prima facie obvious in the absence of evidence to the contrary.

12. No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

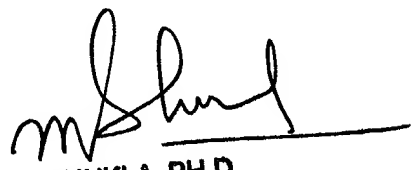
Please note that effective January 13, the offices for Examiner Shukla, SPE Reynolds and LIE William Phillips will move to the new USPTO location in Alexandria, VA and their phone numbers will change. The new phone numbers will be as follows:

Ram Shukla: **(571) 272-0735**

Deborah Reynolds: **(571) 272-0734**

William Phillips: **(571) 272-0548**

Ram R. Shukla, Ph.D.  
Primary Examiner  
Art Unit 1632



**RAM R. SHUKLA, PH.D.**  
**PRIMARY EXAMINER**